REMARKS

I. Status of the claims

After amendment, Claims 62, 102, 103, 105-107, 110, 113, 114, 119-121, 123-137, and 140-148 are pending in the instant application. Applicants thank the Examiner for the careful review of the claims. Non-compliant markings noted by the Examiner in claims 106, 107, and 141 have been corrected. Claim 111 has been cancelled without prejudice, and claims 107, 114, 123, 124, 129-133, 137, 141, and 143-148 have been amended as described below. No new matter is added by these amendments.

II. Claim Objections

Claims 110, 111, 113, 114, 123, 124, 132, 133, 137, 141, 142, and 144-148 are objected to. The following informalities have been addressed by amendment to more particularly point out Applicants' invention.

(1) In each of claims 110, 111, 113, and 132, the preamble of the claim lacked proper antecedent basis for the term "protein". This objection has been mooted by amending the parent claim 107 to recite "protein" as in the other independent claims, rather than "recombinant protein." In addition, Claim 111 has been cancelled.

(2) Claim 114 is objected to for referring to "recombinant protein" which did not occur in some of the parent claims. This rejection has also been mooted by amending "recombinant protein" to "protein."

(3) In each of claims 123, 124, 132 and 133, the term pCD4Hγ1 has been changed to pCD4-Hγ1 (i.e., hyphenated, as in the specification).

(4) Claims 137, 146, and 148 are objected to for referring to "recombinant protein." This objection has also been mooted by amending the claims to refer to the "protein" of the parent claims.

(5) In Claims 141, 142, and 144, commas have been added after the introductory phrase.

(6) The term "IgG1" has been rewritten as "IgG_1" in claims 145 and 147.

In view of the above, Applicants submit that the informalities noted in the claims have been addressed.

III. Claim Rejections – 35 USC §112, 4th paragraph

The Examiner noted that Claim 111 was of improper dependent form because it fails to further limit the subject matter of parent claims 107 and 110. Claim 111 has been cancelled, thereby mooting this rejection. Applicants therefore request withdrawal.

IV. Claim Rejections – 35 USC 103

Claims 62, 102, 103, 105-107, 110, 113, 114, 119-121, 123-137, and 140-148, are rejected under 35 USC § 103(a) as allegedly unpatentable over U.S. Patent 5,395,760 (Smith et al.), and further in view of U.S. Patent 5,428,130 (Capon et al.).

Smith et al. is cited for teaching the p75 TNF receptor (TNFR) and a number of proteins and analogs starting at column 7, line 8 and continuing for several columns of text. Office Action at 5-6. The Action cites text in Smith et al. that describes a soluble TNF receptor, and various monovalent and polyvalent forms of TNFR (Smith et al. column 9, line 17 to column 10, line 68). Office Action at 6-7. In particular, Smith et al. is relied upon for teaching a chimeric antibody molecule in which "TNF-R sequences [are] substituted for the

variable domains of either or both of the immunoglobulin molecule heavy and light chains and having unmodified constant region domains." Office Action at 7. As the Examiner notes, Smith et al. does not teach fusion proteins missing the first domain of the heavy chain constant region (C_H1).

Capon et al. teaches a large number of hybrid immunoglobulins comprising a ligand-binding portion of a receptor and a portion of an immunoglobulin (Ig). Among these configurations, the Examiner cites the tetramer structure shown in column 11 that encompasses the chimeric antibody molecules taught by Smith et al. Office Action at 8. The Examiner also cites to a teaching in column 15 of Capon et al. which describes two preferred embodiments of a hybrid immunoglobulin comprising the N-terminal portion of a lymphocyte homing receptor (LHR); one containing the entire heavy chain constant region, and one missing the C_H1 domain. Finally, the Examiner cites to a specific example of a LHR-Ig fusion protein in Example 4. Office Action at 8.

The Examiner asserts that it would have been obvious to one of ordinary skill to replace the unmodified constant region of the chimeric antibody taught by Smith et al. with one of the embodiments described for the LHR-Ig hybrid. Office Action at 9. The Examiner inexplicably further asserts that the "lack of the first constant region domain would result in the lack of inclusion of an immunoglobulin light chain in the final molecule." Office Action at 10. The Examiner states that the person of ordinary skill would use the resulting fusion protein for any of the TNF-binding uses taught by Smith et al. or for "purification of the TNF-R sequences, as Smith et al. teach that fusion proteins can be used for TNF-R purification, and Capon et al. teach that immunoglobulin fusion proteins can be used for ligand binding partner purification." Office Action at 9-10. The Office Action also asserts a reasonable expectation of success in making this substitution of one known element for use in an immunoglobulin fusion protein for another known element to achieve predictable results. Office Action at 10.

As with the previous rejection based on Dembic et al. and Capon et al. that was reversed by the Board of Patent Appeals and Interferences in Appeal 2009-014889, the new combination of cited references fails to render the instantly claimed invention obvious. In

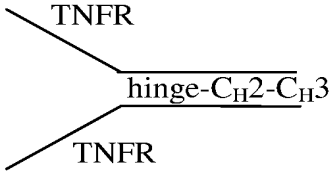
fact, the current rejection leads one of ordinary skill even further away from the claimed invention and, therefore, the prior holding by the Board applies with even more force to the new, weaker rejection. Smith et al. and Capon et al. together teach a structurally different embodiment that leads away from the claimed invention. Only hindsight would direct one of ordinary skill to select and then modify that embodiment in order to reach the claimed invention. Finally, even if one assumes a *prima facie* case, Applicants' overwhelming evidence of unexpected properties mandates the same conclusion of nonobviousness.

A. The Board's Decision Reversing the Previous Obviousness Rejection Also Applies To the New Rejection

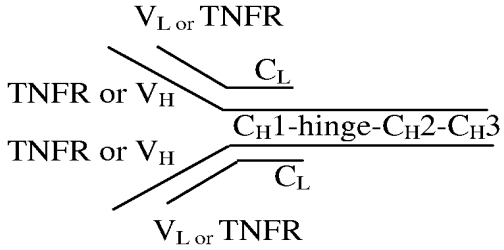
The current obviousness rejection based upon Smith et al. and Capon et al. is even further removed from the claimed invention than the prior obviousness rejection that was recently overturned by the Board. Capon et al. is common to both rejections[1], and teaches a large variety of immunoglobulin fusion molecules containing a ligand-binding portion of a receptor. Both Dembic et al. and Smith et al. teach the ligand-binding portion of the p75 TNF receptor molecule.

The difference between the two rejections is that the Examiner now relies upon Smith et al. for teaching a "chimeric antibody molecule" comprising two heavy and two light chains, in which the variable regions of either or both of the heavy and light chains are replaced with a TNFR sequence. Office Action at 7 and 9-10. However, this chimeric antibody molecule (diagrammed below) differs from the claimed invention in that it has a C_H1 domain contained within the heavy chain, and also has a full light chain.

[1] US Patent 5,128,130 (which is currently cited) is a continuation of a continuation of US Patent 5,116,964 (which was cited in the rejection that was the subject of the appeal), and these patents therefore share the same disclosure.

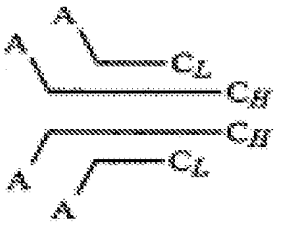


Claimed Molecule



Chimeric antibody molecule of Smith et al.

Capon et al. also describe an identical "preferred" embodiment where "hybrid immunoglobulins of this invention are also constructed in a fashion similar to ***chimeric antibodies*** in which a variable domain from an antibody of one species is substituted for the variable domain of another species." Capon et al., col. 15, lines 9-25 (emphasis added); and col. 5, lines 37-41 ("preferred"). The Examiner acknowledges the identity of the Smith et al. and Capon et al. disclosures, stating that the tetramer structure shown in column 11 of Capon et al. encompasses the chimeric antibody molecules taught by Smith et al. (Office Action at 8):



Preferred hybrid immunoglobulin of Capon et al.

Without the disclosure of Smith et al. (as in the prior combination of Dembic et al. and Capon et al.), one of skill in the art would be confronted with the myriad of different formats for Ig/ligand binding fusion proteins disclosed in Capon et al. with no guidance as to which to choose. ***With*** the additional disclosure of Smith et al., one of skill in the art would be directed to a particular format from among this myriad of possibilities, a format that is outside the scope of the claims. Given this direction, one of skill in the art is led in a different direction that is even further away from the claimed invention.

Additionally, Smith et al. teaches away from selecting the particular combination recited in the instant claims because it requires the antibody to "hav[e] *unmodified constant region domains*." Smith et al., col. 10, ln. 56-57. An unmodified constant domain of an antibody contains both heavy and light chain sequences and assembles into a tetramer. Given this explicit teaching to *not* modify the constant domain, one of ordinary skill in the art would be led away from arriving at the protein recited in the current claims, which contains "all the domains of the constant region of an immunoglobulin heavy chain other than the first domain of said constant region" and assembles into a dimer.

The Board held that "Appellants' evidence of unexpected results is convincing to rebut the Examiner's obviousness rejection" based upon Dembic et al. and Capon et al. Appeal 2009-014889, Decision on Appeal at 7. Appellants' claimed invention was clearly non-obvious in view of this combination, under which the ordinary skilled artisan would have been confronted with all of the possibilities for an immunoglobulin fusion protein described in Capon et al. For the numerous reasons above, the teachings of the new combination of references direct one of skill in the art even further away from the claimed invention than the prior combination already considered by the Board. Accordingly, the Board's conclusion of non-obviousness applies with even greater force to the new obviousness rejection.

B. The Structural Differences Between the Claimed Invention and the Molecules Taught by the Cited Art

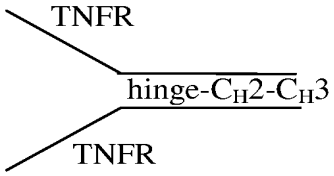
The claimed invention is a novel combination of components – a soluble fragment of p75 TNFR, fused to the hinge, C_H2 and C_H3 domains of a human IgG antibody, wherein the protein binds human TNF. This resulting fusion protein forms a homodimer through disulfide bonds within the hinge domain. The components of the fusion protein together each function in a way that is completely different from what would have been predicted. For example, the TNFR portion of the combination binds to TNF differently, showing unexpected binding kinetics, affinity and stoichiometry. The immunoglobulin portion of the combination lacks the effector functions and aggregation ability that it was predicted to retain.

As noted by the Examiner, Smith et al. discloses a large number of different fusions, analogs, and multimers in columns 7 through 10, both monovalent (i.e. one TNF-binding domain) and multivalent (i.e., multiple TNF-binding domains). Office Action at 6-7. The Examiner acknowledges that none of these alternatives correspond to the claimed invention. Office Action at 8. Without an explanation for selecting multivalent embodiments, much less embodiments comprising antibody sequence, the Examiner cites to a portion of Smith et al. which describes chimeric antibodies:

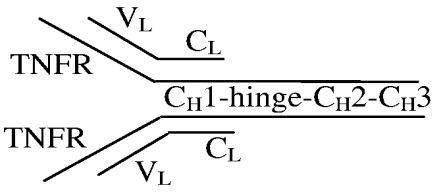
> A recombinant chimeric antibody may also be produced having TNF-R sequences substituted for the variable domains of either or both of the immunoglobulin molecule heavy and light chains and having unmodified constant region domains. For example, chimeric TNF-R/IgG1 may be produced from two chimeric genes – a TNF-R/human κ light chain chimera (TNF-R/Cκ) and a TNF-R/human γ1 heavy chain chimera (TNF-R/Cγ-1). Following transcription and translation of the two chimeric genes, the gene products assemble into a single chimeric antibody molecule having TNF-R displayed bivalently. Such polyvalent forms of TNF-R may have enhanced binding affinity for TNF ligand. Additional details relating to the construction of such chimeric antibody molecules are disclosed in WO 89/09622 and EP 315062. [Col. 10, lines 53-68, Smith et al.]

The Examiner acknowledges that this disclosure provides three alternatives (TNF-R substituted for "either or both" of the variable regions of Ig heavy and light chains, with either two or four TNF-binding sites), and also acknowledges that, due to disulfide bonding between the heavy chains and light chains, the resultant fusion proteins form a tetrameric structure. Office Action at 7.

Again without explanation, the Examiner apparently selects from among these three alternatives the embodiments containing two, rather than four, TNF-binding sites; and from among the two remaining options with two TNF-binding sites, the Examiner selects the option containing a TNF-R-C_H1-Hinge-C_H2-C_H3 amino acid chain and a V_L-C_L amino acid chain. Office Action at 9. As compared to the claimed invention, this embodiment can be diagrammed as follows:



Claimed molecule



Examiner's starting structure

The claimed molecule differs from the Examiner's starting structure in that it (1) lacks the light chains entirely and (2) lacks the C_H1 domains of the IgG heavy chains. The resulting protein of the claimed invention therefore has different disulfide bonding, and assembles as a homodimer, instead of the tetramer described in Smith et al.

While the Examiner acknowledges that even this starting structure of Smith et al. differs from the claimed invention, the Examiner asserts that one of ordinary skill would have modified this starting structure to arrive at the claimed invention. The asserted case of *prima facie* obviousness, then, rests upon the selection of this particular starting structure together with motivation to modify this starting structure to arrive at the claimed invention. This asserted *prima facie* case fails to pass muster, for the reasons described below.

C. Selection of the Starting Structure Is Based Only On Hindsight

It is the Examiner's burden to establish a *prima facie* case of obviousness. Doing so requires a clear articulation of the rationale for obviousness, and the factual findings supporting the rationale. In particular, where the obviousness case relies upon selection and modification of a prior art embodiment or "lead compound", as it does here, the Examiner must explain the ***specific reason to select*** the lead compound, *and* ***the specific reason for modifying*** this prior art compound, as well as the predictability of the result. See the "Examination Guidelines Update: Developments in the Obviousness Inquiry After KSR v. Teleflex", 75 *Fed. Reg.*, No. 169, page 53643 et seq., September 1, 2010 ("2010 KSR Guidelines Update"), e.g., page 53652, 1st col. ("there must be some reason 'to select and modify a known compound'").

Here, the Examiner has provided no reason why one of ordinary skill would select the particular starting structure from Smith et al. from among the many different "Proteins and Analogs" acknowledged in the Office Action. If the rationale is to make a protein for "any of the TNF-binding uses taught by Smith", then any of the many different analogs, fusion proteins and conjugates taught in Smith could be chosen.

If the rationale is to make a molecule for "ligand binding partner purification" as taught by Capon et al., then any of the polyvalent and monovalent forms taught in Smith et al. could be chosen. For example, Smith et al. describes:

> Both monovalent forms and polyvalent forms of TNF-R are useful in the compositions and methods of this invention. Polyvalent forms possess multiple TNF-R binding sites for TNF ligand. For example, a bivalent soluble TNF-R may consist of two tandem repeats of amino acids 1-235 of FIG. 2A, separated by a linker region. . . . Alternatively, TNF-R may be chemically coupled to biotin, and the biotin-TNF-R conjugate then allowed to bind to avidin, resulting in tetravalent avidin/biotin/TNF-R molecules. TNF-R may also be covalently coupled to dinitrophenol (DNP) or trinitrophenol (TNP) and the resulting conjugate precipitated with anti-DNP or anti-TNP-IgM, to form decameric conjugates with a valency of 10 for TNF-R binding sites. [Smith et al., col. 10, lines 33-52]

Thus, Smith et al. describes many different embodiments useful for purification. *See also* Smith et al., col. 7, lines 54-68. The Examiner has provided no reason why one of ordinary skill would have selected the hypothetical chimeric antibody molecules, in particular, from among the many forms described. The other polyvalent forms, including forms with 10 TNF-Rs, could have potentially been more useful than a form with only two TNF-Rs. For *in vitro* uses such as purification, there would be no reason to select an embodiment that would be expected to have increased half-life *in vivo,* which was one primary object of the embodiments taught by Capon et al. *See* Capon et al., col. 1, lines 13-16.

Furthermore, the Examiner provided no reason why one of ordinary skill would select embodiments that had two rather than four TNF-R binding domains, from among the three different types of chimeric antibodies described in Smith et al.. Nor did the Examiner provide a reason for choosing the particular starting structure

diagrammed above, from among the two options with two TNF-R binding domains (i.e., where either light or heavy chain variable regions were replaced with TNF-R sequence). Accordingly, the only possible reason for picking the "chimeric antibody" structure from Smith et al. is hindsight.

D. There was No Reason to Modify the Starting Structure so as to Achieve the Claimed Invention

Even if one of ordinary skill in the art had a reason to pick the cited starting structure, this person would still need to have an incentive to modify it to reach the claimed invention. These modifications include (a) removing the entire light chain, including the light chain variable domains and the light chain constant domains, and (b) removing a portion, the first constant domain C_H1, of the heavy chain.

Without identifying a particular need for improvement, problem to be solved or design incentive prompting modification of the chimeric antibody molecule, the Examiner asserts that the person of ordinary skill in the art would be motivated to make such modifications. The stated reasons were that (1) Capon et al. teach the modified heavy chain constant region lacking the first domain of the constant region as an alternative preferred embodiment for use in constructing fusion proteins between ligand binding portions of a receptor and immunoglobulin proteins, and (2) making such a substitution would obviate the need for co-expression of immunoglobulin light chains resulting in a simpler system requiring expression of a single component. Office Action at 9. This reasoning fails because it misstates the teachings of the cited art, omits any factual support for the assertions, and ignores the reasons of record why one of ordinary skill would ***not*** make such a modification.

Capon et al. displays over two hundred and fifty different general formats for Ig/ligand binding protein fusions, which are completely unlimited with respect to the identity of the ligand binding portion of the fusion protein. Capon et al., col. 11, line 1 to col. 14, line 40. In total, the disclosure in Capon et al. encompasses at least thousands of fusion proteins. Capon et al. discloses fusion of receptor fragments to immunoglobulin constant domains,

light and/or heavy, and including monomeric, homodimeric, heterodimeric, trimeric, tetrameric, homomultimeric and heteromultimeric forms.

Contrary to the implication in the Office Action at 9, the cited portion of Capon et al. does not teach the modified heavy chain constant region lacking the $C_H1$domain as an "alternate preferred embodiment" for constructing fusion proteins ***in general.*** Instead, Capon et al. mentions this configuration as an alternative embodiment ***only*** in the context of ***providing effector function to LH receptor fusion proteins***.

> A particularly preferred embodiment is a fusion of an N-terminal portion ***of a LHR***, which contains the binding site for the endothelium of lymphoid tissue, to the C-terminal Fc portion of an antibody, ***containing the effector functions of*** immunoglobulin G_1. There are two preferred embodiments of this sort; in one, the entire heavy chain constant region is fused to a portion of the LHR; in another, a sequence beginning in the hinge region just upstream of the papain cleavage site which defines IgG Fc chemically (residue 216, taking the first residue of heavy chain constant region to be 114 [Kabat et al., "Sequences of Proteins of Immunological Interest" 4th Ed., 1987], or analogous sites of other immunoglobulins) is fused to a portion of the LHR. [Capon et al., col. 14, line 61 to col. 15, line 7]

Accordingly, the Examiner relies on an embodiment that is only "preferred" in the case of the LH receptor fusions for providing effector functions. However, this teaching has no particular relevance to the asserted rationale of using the molecule for ligand binding partner purification, since there would be no need to supply effector functions for such an *in vitro* use.

Although the Examiner cited Example 4, the Examiner ignored the alternative working example in the application, Example 5, addressing construction of a human CD4-Ig fusion protein. In this example, Capon et al. states that "The CD4-Ig plasmid is that described in Capon et al., supra, modified by the ***deletion*** of the coding region for the CH1 domain and ***a portion of the hinge region***. . . [emphasis added]." The ordinary skilled artisan following the teaching of Example 5, rather than Example 4, would have arrived at an embodiment ***outside*** the scope of the pending claims, i.e. missing a portion of the hinge domain.

There is no general preference for an embodiment in which the immunoglobulin portion contains all of the domains of the constant region of a human immunoglobulin IgG heavy chain other than the first domain of said constant region. Applicants' inspection revealed no such embodiment highlighted in the "Summary of the Invention" (Capon et al., col. 5, line 14 to col. 6, line 22) or in the description of more than 250 generic formats for fusion proteins disclosed in columns 11-14 of Capon et al. In fact, col. 10, lines 9-12, of Capon et al. states that "***Ordinarily***, the ligand binding partner is fused C-terminally to the N-terminus of the constant region of immunoglobulins in place of the variable region(s) thereof. [Emphasis added.]" Thus, there is no reason other than hindsight to select a particular modified heavy chain constant region. Nor is there an articulated reason for ignoring the explicit statement in Smith et al. that the constant region be "unmodified," which directly contradicts substitution of this particular modified constant region into the chimeric antibody of Smith et al.

Moreover, even if the ordinary skilled artisan had been prompted to remove the $C_H1$domain from a hybrid immunoglobulin IgG1 protein, there was no reason to further modify the protein by removing the light chain which is covalently disulfide-bonded to the hinge domain of IgG1. The Examiner cited to no evidence suggesting that there was a problem with expressing chimeric antibody molecules containing both heavy and light chains, which might be solved by removing the light chains. Applicants respectfully request that this factual assumption be supported by a reference or by a personal affidavit as required under 37 C.F.R. § 1.104(d).

Creating a simpler system is not a specific reason for modifying the starting structure to reach Applicants' claimed invention. If one of ordinary skill wanted to create a simpler system, one could use just a C_H3 domain, or a C_H2 and a C_H3 domain, without a hinge domain. In fact, if one were searching for a "simpler system," one would have preferred the bivalent tandem repeat described in Smith et al. and cited by the Examiner at page 10 of the Office Action. This form would be much preferred over the extra 450+ amino acids required for a dimeric Ig fusion. Thus, mere "simplification of the system" leads to no particular modification, and certainly does not lead to the specific claimed combination of the instant

invention. Hence, the Office Action fails to establish a credible reason why one of ordinary skill in the art would modify the cited starting structure to reach the claimed invention.

There are a number of other embodiments that would have been more preferred than the structure of the claimed invention. For therapeutic uses of a molecule such as TNFR, which was expected to suppress inflammation, one of ordinary skill would have preferred a fusion that did not comprise the hinge-C_H2-C_H3, which is taught to provide pro-inflammatory effector functions. Smith et al., col. 16, lines 60-66; Capon et al., col. 4, lines 45-49. For non-therapeutic uses, the teachings of Capon et al. regarding two of the primary motivations for immunoglobulin fusions, enhanced plasma half-life and retention of effector functions, would be completely irrelevant. Capon et al., col. 1, lines 13-16.

For these *in vitro* uses there would have been a better rationale for selecting a monomeric form missing the hinge region, in order to maximize the likelihood of binding to trimeric TNF. Monomeric forms would have been preferred because dimeric or other multimeric forms may have had a spatial geometry that prevented high affinity binding to the trimeric TNF ligand, as stated in the Declaration Under 37 C.F.R. 1.132 of Dr. Werner Lesslauer submitted with Amendment and Request for Reconsideration dated January 12, 2005 and originally signed by Dr. Lesslauer on October 8, 2001 ("Lesslauer Declaration A"). The Lesslauer Declaration A contradicts the Examiner's allegation that one of ordinary skill in the art would expect the resultant fusion protein to function. Office Action at 10. If one desired increased valency for *in vitro* uses, any of the other embodiments described in Smith, including the tandem repeat format cited by the Examiner, or embodiments with higher valency such as 10 TNF-binding sites, would have been preferred.

In addition, as noted above in section A, the cited combination of references teaches away from modifying the "chimeric antibody molecule" of Smith et al., which is also a generically preferred fusion of Capon et al. MPEP §2144.08 states that the Examiner is obligated to "consider any teaching or suggestion in the reference of a ***preferred species or subgenus that is significantly different in structure from the claimed species or subgenus***. Such a teaching may weigh against selecting the claimed species or subgenus and thus ***against*** a determination of obviousness." MPEP §2144.08(II)(A)(4)(c) (citing *In re Baird*, 16

F.3d at 382-83). MPEP §2144.08 also cites *Baird* for the guidance that "teachings of preferred species of a complex nature within a disclosed genus may motivate an artisan of ordinary skill to make similar complex species and thus teach away from making simple species within the genus." MPEP §2144.08(II)(A)(4)(c) (citing *In re Baird*, 16 F.3d at 382).

Thus, there were many reasons to prefer embodiments *other than* those recited in the claims, and the cited references *teach away* from the particular embodiments recited in the claims. In view of all of the reasons discussed above, the Examiner has failed to establish a proper *prima facie* case of obviousness.

E. The Unexpected Results Found Compelling By the Board Mandate a Conclusion of Non-Obviousness

The Office Action makes no reference to Applicants' previously submitted evidence of unexpected results for multiple embodiments within the scope of the instant claims. The evidence shows that both parts of the claimed fusion protein function differently from the way they function in other contexts. The TNF-R portion binds TNFα with greater kinetic stability and unexpected stoichiometry, and more effectively neutralizes the activity of TNFα. The immunoglobulin portion lacks expected effector functions in a number of different categories. The combination also functions differently than predicted because it lacks aggregation ability. Thus, the claimed invention is not merely the substitution of one known element for another to obtained predictable results—Applicants have demonstrated ***unexpected*** results that were completely different from what had been predicted. These unexpected results have been acknowledged as such by both the Examiner and the Board of Patent Appeals and Interferences.

The Examiner has agreed that that the evidence of improved kinetic stability, increased TNF neutralization potency, failure to form aggregating complexes, and drastically reduced effector function were unexpected results. Examiner's Answer dated March 24, 2009 at pages 62, 63, 64 and 65. The Board concluded that these unexpected results overcame the Examiner's previous obviousness rejection based on the combination of Dembic et al. and Capon et al. For the reasons explained above in section A, the new

combination of Smith et al. and Capon et al. together teach an embodiment that is outside the scope of the pending claims and thus leads one of ordinary skill in the art farther from the claimed invention than the prior combination of Dembic et al. plus Capon et al. Accordingly, the Board's determination that the evidence of unexpected results is convincing to rebut the obviousness rejection is all the more controlling here.

Applicants previously provided evidence that hybrid immunoglobulin fusion proteins comprising the hinge, C_H2 and C_H3 domains were expected to retain effector functions. *See, e.g.,* the teaching of Capon et al., col. 4, lines 45-49, and col. 14, lines 61-68. It was well known that the binding sites for the proteins that initiate ADCC and CDC (FcγRs and C1q, respectively) are within the C_H2 domain, for C1q, or in the region linking the hinge to C_H2 domains, for FcγRs. *See, e.g.,* Capon, *Nature* 337: 525-531, 1989, at page 528, 1st col. (submitted as item C175 on SB/08 dated October 3, 2006). Consistent with this teaching and expectation, prior art references confirmed that dimeric fusion proteins consisting of hinge, C_H2 and C_H3 domains fused to CD4 fragment retain effector functions.[2]

In contrast to this established expectation, Applicants provided uncontested evidence that p75 TNFR-immunoglobulin fusion proteins within the scope of the claims exhibited unexpected properties in a number of different categories, including FcγR-binding, C1q-binding, ADCC, CDC, and aggregation ability. One such protein consists of the extracellular domain of p75 TNFR linked to the hinge, C_H2 and C_H3 domain, but not the $C_H1$domain, of IgG1. *See* Mohler et al., J. Immunol. 151: 1548-1561, 1993 (submitted as item C162 on SB/08 dated October 3, 2006); Kohno et al., Presentation 1495, poster 271, presented at American College of Rheumatology Annual Meeting, Nov. 13-17, 2005, San Diego, CA (submitted as item C171 on SB/08 dated October 3, 2006); Khare et al., Poster 715 presented at the Annual Meeting of the Society for Investigative Dermatology (SID), May 3-5, 2006, Philadelphia, PA (submitted as item C177 on SB/08 dated October 3, 2006); Declaration of Taruna Arora Under 37 C.F.R. 1.132 ("Arora Declaration," paragraphs 3-6, Exhibits C and D, submitted as item E3 on SB/08 dated December 16, 2010) and Barone et al., Arthritis

[2] See Byrn et al., *Nature* 344: 667-670, April 1990 at page 668, 1st col., and Fig. 2 at page 669 (ADCC retained); Traunecker, *Nature*, 339:68-70, 1989 at page 69, 1st col. and Fig. 3 (FcγR and C1q binding retained).

Rheum., 42(9) Suppl, September 1999 (submitted as item C176 on SB/08 dated October 3, 2006).

For example, etanercept displayed ***markedly reduced levels of ADCC*** as compared to a TNF-binding antibody. Figure 3 of Khare; also Exhibit D of Arora Declaration. Since ADCC is pro-inflammatory, the absence or marked reduction in this activity is advantageous when treating inflammatory disorders. The Barone reference reports that etanercept is ***unable to mediate CDC***. Data in the Arora Declaration shows that etanercept exhibits no detectable CDC activity at most concentrations (5/7) tested, and markedly reduced CDC activity at the two highest concentrations. Exhibit C of Arora Declaration. Figure 4 of Khare also shows that etanercept exhibits markedly reduced CDC activity. Since CDC is pro-inflammatory, the absence or marked reduction in this activity is also advantageous when treating inflammatory disorders.

As noted above, one of the working examples in Capon et al. instructs preparation of an embodiment modified by "the deletion of . . . a portion of the hinge region up to the first cysteine residue." Col. 44, lines 59-62. The Arora Declaration compares embodiments missing a portion of the hinge domain (missing the first five amino acids EPKSC of the hinge) to etanercept, and confirms that etanercept shows unexpected properties compared to such embodiments that fall outside of the scope of Applicants' claims. This is further proof that the claimed combination results in embodiments with unique and unexpected properties.

Moreover, it is likely that at least some of these unexpected properties of etanercept correlate to differences in clinical efficacy and safety between etanercept and anti-TNF-α antibodies. Researchers in the field have drawn links between differences in binding stoichiometry/effector function and differences in clinical efficacy and safety. Granulomatous infectious diseases occur at a greater frequency in patients treated with infliximab, an anti-TNF-α antibody, as compared to patients treated with etanercept. Wallis et al. (2004), Clin. Inf. Dis. 38: 1261-1265 at 1262-1263; Wallis et al. (2005), Clin. Inf. Dis. 41(Suppl 2): S1-S5 at S2-S4 (documents D5 and D6 in SB/08 submitted herewith). With regard to this observed difference, one group of researchers comments, "[I]t is possible that the combination of high avidity binding to mTNF within the granulomatous tissue, and the

ability to bind FcγR and C1q as large Ab complexes, may account for the higher rates of granulomatous infections in patients treated with the anti-TNF mAbs." Arora et al. (2009), Cytokine 45: 124-131. page 130, right col.(emphasis added) (document D1 in SB/08 submitted herewith). Other authors have made the following observations:

> Infliximab induces complement-dependent cytolysis and antibody-dependent cell-mediated cytotoxicity in a murine myeloma cell line expressing membrane-associated TNF (67). Macrophages and monocytes are among the cells that express membrane-associated TNF. The monocytopenia observed in patients following treatment with infliximab that can persist for weeks following infusion (68) may reflect direct killing of cells expressing membrane-associated TNF by infliximab. This has clinical implications because monocytes are an essential component of granulomas; monocyte elimination might lead to susceptibility to granulomatous diseases. , , , Etanercept contains the Fc portion of IgG1, but reportedly ***does not fix complement*** (69), perhaps because steric hindrance prevents C1q binding, which initiates the classical complement cascade. Furthermore, because etanercept ***binds only single molecules of TNF, it is unlikely to form aggregates*** that can activate complement-dependent cytolysis and antibody-dependent cell-mediated cytotoxicity. [Emphasis added.]

Furst et al. (2006), Semin. Arthritis Rheum. 36: 159-167, at page 164, left col. (document D2 in SB/08 submitted herewith).

Clinicians have also commented on the possible relationship between molecular mechanisms of action and efficacy and safety profiles, in particular, reactivation of herpes zoster and tuberculosis. Strangfeld et al. (2009), JAMA 301(7): 737-744 at 743 middle col. (document D4 in SB/08 submitted herewith). Thus, some of the properties that Applicants have reported as unexpected results have been hypothesized by researchers to be related to the different clinical efficacy and safety profiles of anti-TNF-α antibodies as compared to etanercept.

In summary, the Office Action fails to set forth a *prima facie* case of obviousness. The only incentive to choose the starting structure cited from Smith et al. is hindsight, and one of ordinary skill would be motivated *against* altering that starting structure to reach the claimed invention. In addition, Applicants have submitted overwhelming, uncontradicted evidence showing that the claimed fusion proteins have unexpected properties in more than

six different categories, such as TNFα binding and inhibition (Lesslauer Declaration A), FcγR-binding, C1q-binding, ADCC, CDC, aggregation ability and binding stoichiometry. Researchers in the art have opined that some of these unexpected properties may be related to the clinical safety and efficacy profile of etanercept. As with the previous rejection based on Dembic and Capon et al. that was overturned by the Board of Patent Appeals and Interferences, Applicants' demonstration of unexpected results rebuts the outstanding obviousness rejection. Applicants respectfully request that the rejections be withdrawn and the instant claims proceed to issuance.

F. Claims Directed to Pharmaceutical Compositions Are Not Obvious

Claims 114, 137, 146, and 148, which are directed to pharmaceutical compositions, are also rejected as obvious. The Office Action states that the recitation of "pharmaceutical composition" is accorded no patentable weight because it appears in the preamble. Office Action at 12. This position contravenes established case law. A claim's preamble must be read as a meaningful limitation when it distinguishes over the prior art, and when it results in a physical difference in the product claimed. See *Catalina Mktg., Int'l, Inc. v. Coolsavings.com, Inc.*, 289 F.3d 801, 808-809, 62 U.S.P.Q.2ds 1781, 1787 (Fed. Cir. 2002) (reliance on the preamble during prosecution to distinguish the claimed invention from the prior art transforms the preamble into a claim limitation); *see In re Stencel*, 828 F.2d 751, 4 U.S.P.Q.2d 1071 (Fed. Cir. 1987); *see also* MPEP §2111.02 ("During examination, statements in the preamble reciting the purpose or intended use of the claimed invention must be evaluated to determine whether the recited purpose or intended use results in a structural difference . . . If so, the recitation serves to limit the claim.")

Further, Applicants dispute the factual basis for the Office Action's statement that a person of ordinary skill in the art would be motivated to include a pharmaceutically acceptable carrier because "[r]esuspending the protein in a composition comprising a pharmaceutically acceptable carrier would allow the composition to retain versatility in any of the uses taught by Smith et al or Capon et al. (i.e. purification or administration)." Office Action at 12-13. Applicants provide further evidence herewith that pharmaceutical compositions are subject to strict requirements for sterility, sterile handling during

manufacturing, and pyrogenic levels. (See Avis in *Remington Pharmaceutical Sciences*, Chapter 85, pp. 1518-1541 (1985); FDA Guidelines on Sterile Drug Products Produced by Aseptic Processing (1987), documents D8 and D9 in SB/08 submitted herewith) These safeguards are costly, require significant effort and vigilance, and would not have been followed when making a reagent used for purification. If the Examiner has evidence otherwise, he is respectfully requested to make such evidence of record.

CONCLUSION

Applicants believe all pending claims are in condition for allowance. If further discussion or amendments would expedite allowance of the claims, the Examiner is asked to contact the undersigned at the number below.

Dated: March 29, 2011

Respectfully submitted,

By: /Li-Hsien Rin-Laures Reg. 33,547/
Li-Hsien Rin-Laures
Registration No.: 33,547
MARSHALL, GERSTEIN & BORUN LLP
233 S. Wacker Drive, Suite 6300
Sears Tower
Chicago, Illinois 60606-6357
(312) 474-6300
Attorney for Applicant